Sleep Medicine Reviews 18 (2014) 399–404

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Cardiovascular implications of obstructive sleep apnea associated with the presence of a patent foramen ovale

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ARTICLE INFO

Article history:
Received 25 May 2013
Received in revised form
29 January 2014
Accepted 5 February 2014
Available online 13 February 2014

Keywords:
Patent foramen ovale
Obstructive sleep apnea
Cardiovascular disease
Stroke
Percutaneous closure

SUMMARY

Patent foramen ovale (PFO) is a common congenital cardiac abnormality of the atrial septum which occurs in 25% of the population. It allows communication between the right and left atrium enabling right to left shunting of deoxygenated blood (after birth) which may be linked to strokes or transient ischemic attacks. PFO may also have an association with obstructive sleep apnea (OSA).

OSA is a common medical condition occurring in 9% of adult males and 4% of adult females. It may increase the risk of cardiovascular disease. OSA causes intermittent hypoxia from episodes of apnea and hypopnea during sleep. Consequently, hypoxic pulmonary vasoconstriction ensues which produces an increased right atrial pressure which may generate a right to left shunt during apneic episodes promoting the occurrence of thromboembolic events. The existence of a PFO may be higher in patients with OSA. The presence of a PFO and OSA may increase the risk of stroke. In this review, the association of PFO and OSA is described along with their implications for cardiovascular disease. The relevant literature and treatment options are discussed to elaborate on the significance of the associated pathology.

Introduction

Patent foramen ovale (PFO) is a common congenital cardiac anatomical variant of the atrial septum which occurs in 25% of the population [1,2]. A PFO allows communication between the right and left atrium enabling right to left shunting of oxygenated blood in utero, thereby, bypassing the high resistance fetal pulmonary circulation [3]. After birth, the rise in the left atrial pressure with a decline in the right atrial pressure and pulmonary vascular resistance enables closure of the PFO [2,3]. PFO closure is initially functional and by the first or second year of life it becomes anatomically sealed in most children. The size of PFOs increases with age while the prevalence decreases with age [3]. PFOs may be linked to strokes, transient ischemic attacks (TIAs), migraines, systemic embolism, or decompression illness [1,3,4]. Furthermore, PFO may have an association with obstructive sleep apnea (OSA) [1].

OSA is a common medical condition occurring in 9% of adult males and 4% of adult females [3]. OSA may occur in 5–15% of the middle-aged population and may increase the risk of cardiovascular disease [5]. OSA causes nocturnal repetitive collapse of the pharyngeal airway which causes a decrease or cessation of airflow [3]. Intermittent hypoxia caused by an obstructive event during sleep induces hypoxic pulmonary vasoconstriction which increases the pulmonary vascular resistance and also produces an increased right atrial pressure. Thus, a right to left shunt is produced which may provide the nidus for systemic embolization [3]. In this review, the association of PFO and OSA is described along with their implications for cardiovascular disease. The relevant literature, clinical research, and case reports are also discussed to elaborate on their associated effects and treatment options.

Definition and prevalence of PFOs

A PFO is a normal communication between the right and the left atria which occurs during fetal development [6]. PFO remains as an embryological remnant of the fetal circulation derived from incomplete fusion of the septum primum and secundum [7]. PFOs are found in 20–34% of the population and its prevalence decreases with age [6]. Most PFOs are benign and shunting is normally not present during rest [7]. However, voluntary maneuvers such as coughing, Valsalva, singing, coitus, or weight-lifting increases the right to left shunting via a PFO [7]. Consequently, thrombi or air may enter the arterial circulation, thereby, inducing a stroke or TIA. Moreover, cryptogenic strokes may occur more often in patients with PFOs compared with the general population (approximately

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http://dx.doi.org/10.1016/j.smrv.2014.02.002
1087-0792/

Abbreviations

AHI apnea–hypopnea index
BIPAP bilevel positive airway pressure
CLOSURE I trial evaluation of the STARFlex septal closure system in patients with a stroke or TIA due to the possible passage of a clot of unknown origin through a patent foramen ovale
CPAP continuous positive airway pressure
OSA obstructive sleep apnea
PC-trial clinical trial comparing percutaneous closure of patent foramen ovale using the Amplatzer PFO occluder with medical treatment in patients with cryptogenic embolism
PFO patent foramen ovale
TIA transient ischemic attack
RESPECT trial randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment
UPPP uvulopalatopharyngoplasty

50–60% vs. 20–25%) [2]. However, no studies have unequivocally linked PFOs to cryptogenic strokes.

Percutaneous PFO closure

Data on the benefits of PFO closure remains controversial. Common reasons for which closure may be considered include cryptogenic stroke (greater than one embolic episode or PFO combined with an atrial septal aneurysm), hypoxia due to right to left intra-cardiac shunting, or major decompression illness in professional divers [1]. Factors which may increase the risk of cryptogenic stroke with PFOs include atrial septal aneurysm, recurrent cryptogenic stroke, large PFO, Chiari network, pulmonary embolism, and prothrombotic states [1].

Complications of PFO closure include device embolization, tamponade, and retroperitoneal bleeding which occur in 1% of cases. Air emboli may also induce transient ST elevation [1]. Long-term complications may include thrombus formation, erosion, and fistula formation [1].

Observational studies of PFO closures

A recent meta-analysis [8] of observational studies comparing percutaneous PFO closure vs. medical therapy for the prevention of recurrent neurological events after cryptogenic stroke showed the superiority of percutaneous closure compared with medical therapy in event reduction [0.8 (95% confidence interval (CI) = 0.5–1.1) vs. 5.0 (95% CI = 3.6–6.9) events/100 person-years]. The meta-analysis included 39 studies (8185 patients) evaluating transcatheter closure, 19 studies (2142 patients) of medical therapy, and 10 studies (1886 patients) comparing both medical and transcatheter closure which were included in a pooled analysis. The pooled analysis showed the incidence of recurrent neurological events/100 patients-years with transcatheter closure of 0.76 (95% CI = 0.48–1.05) compared with 4.39 (95% CI = 3.20–5.59) in the medical therapy group.

Furthermore, treatment with anticoagulants (warfarin) showed lower risk of recurrent neurological events compared with antiplatelet (aspirin or aspirin and clopidogrel) agents [2.2 (95% CI = 1.1–3.4) vs. 4.2 (95% CI = 2.9–5.4)]. Thus, this meta-analysis suggests that PFO closure may be superior to medical management for cryptogenic stroke in patients with evidence of paradoxical embolus.

A systematic review by Khairy et al. [9], also showed a reduction in recurrent neurological thromboembolism with percutaneous closure compared with medical therapy. However, direct comparisons between percutaneous and medical treatment were not provided in this review. Another systematic review by Kitsios et al. [10], compared secondary stroke prevention via PFO closure vs. medical therapy. An analysis of 52 single-arm studies, seven comparative non-randomized studies, and the evaluation of the STARFlex septal closure system in patients with a stroke or TIA due to the possible passage of a clot of unknown origin through a patent foramen ovale (CLOSURE I) trial [11] was performed. The incident rates of recurrent stroke was 0.36 events (95% CI = 0.24–0.56) per 100 person-years with transcatheter closure vs. 2.53 events (95% CI = 1.91–3.35%; $p < 0.001$) per 100 person-years with medical therapy. In observational and non-randomized studies of medical therapy (nine studies), anticoagulants were superior to antiplatelets for the prevention of stroke recurrence (incidence rates of recurrent cerebrovascular events = 0.42, 95% CI = 0.18–0.98).

Randomized controlled trials of PFO closure

The recently completed CLOSURE I trial [12] refutes the findings of the systematic review by Khairy et al. [9] and Kitsios et al. [11] The CLOSURE I trial [12] was the first prospective, multicenter, open-labeled, randomized, independently adjudicated PFO device closure trial which evaluated PFO closure with the STARFlex device (NMT Medical, Boston, Massachusetts) plus medical therapy (six months of aspirin and clopidogrel followed by 18 mo of only aspirin) compared with medical therapy alone (24 mo of warfarin or aspirin or combination therapy) in the prevention of recurrent stroke or TIA in patients with cryptogenic stroke or TIA and a PFO. A total of 909 patients (≤60 y of age) who were followed for two years showed no primary endpoint benefits from percutaneous PFO closure compared with medical therapy [447 patients (5.5%) vs. 462 patients (6.8%); $p = 0.37$] [11]. The primary endpoints were two-year incidence of stroke or TIA, all-cause mortality in 30 d, and neurological mortality 31 d to 2 y. No deaths occurred at 30 d in either group and no deaths from neurological causes occurred within the two-year follow-up in either group. However, the closure group had higher rates of major vascular procedural complications compared with medical therapy [13 (3.2%) vs. 0, $p < 0.001$] and atrial fibrillation [23 (5.7%) vs. 3 (0.7%), $p < 0.001$]. Consequently, the CLOSURE I trial [11] failed to support the benefits of PFO closure with the STARFlex septal closure system in patients with cryptogenic stroke or TIA for the prevention of recurrent stroke or TIA.

Recently, the results of the randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment (RESPECT trial) [13] were reported using the Amplatzer PFO occluder. The RESPECT trial [13] was a prospective, multicenter, randomized, event-driven trial evaluating whether PFO closure was superior to medical therapy (one or more antiplatelet agents or warfarin) in preventing recurrent ischemic stroke or early death. A total of 980 patients (ages of 18–60, mean age of 45.9 y) were enrolled in a 1:1 ratio of medical vs. closure therapy. Treatment exposure between the medical and closure group were unequal due to higher dropout rate in the medical group (1184 patients-years in the medical vs. 1375 patients-years in the closure group; $p = 0.009$). In the intention-to-treat cohort, nine patients in the closure group and 16 in the medical group had a recurrent stroke (hazard ratio with closure, 0.49; 95% CI of 0.22 to 1.11; $p = 0.08$). There were significant variations in the between-group differences in rates of recurrent strokes in the prespecified per-protocol cohort (six events in the closure group vs. 14 events in

the medical group; hazard ratio (HR) = 0.37; 95% CI = 0.14–0.96; $p = 0.03$) and in the as-treated cohort (five events vs. 16 events, medical vs. closure; HR = 0.27; CI = 0.10–0.75; $p = 0.007$). Hence, the study concluded that closure provided no significant benefit in patients who sustained a cryptogenic stroke based upon the intention-to-treat analysis. However, closure was found superior to medical therapy in the prespecified per-protocol and as-treated analysis based upon possible benefit of closure for large shunts or atrial septal aneurysms. Thus, the CLOSURE I trial [11] and the RESPECT trial [13] showed no superiority of PFO closure in the intention-to-treat analysis.

Another recently published trial, the clinical trial comparing percutaneous closure of patent foramen ovale using the Amplatzer PFO occluder with medical treatment in patients with cryptogenic embolism (PC-trial) [14] studied the superiority of PFO closure vs. medical therapy. The primary endpoint of the composite of death, nonfatal stroke, transient ischemia attack, or peripheral emboli occurred in seven out of 204 patients (closure group, 3.4%) vs. 11 of 210 patients (medical group, 5.2%; HR = 0.63%; 95% CI = 0.24–1.62; $p = 0.34$). Thus, the study found no significant reduction of recurrent stroke or death via PFO closure similar to the aforementioned clinical trials.

Consequently, speculation persists about the value of PFO closure given the results of these recent randomized controlled trials which have shown no significant benefits of PFO closure in contrast to the meta-analysis and observational studies which have suggested that PFO closure may be superior to medical therapy. Such contradictory information may be secondary to patient withdrawal from the medical therapy group in the RESPECT trial [13] which may have confounded the results. Moreover, retention and entry bias may have occurred in the study because high risk patients may have been treated outside of the scope of the trial. Nevertheless, patients with larger PFOs or atrial septal aneurysms showed a trend toward benefit from closure in the RESPECT trial [13].

In the CLOSURE trial [11], the two-year follow-up may have been insufficient time to adequately detect the presence of stroke recurrence. The study may also have been underpowered to detect the reduction in stroke rates or the incidence of strokes may have been lower than expected. Also, a precise definition of cryptogenic stroke in clinical practice does not exist which may lead to incorrect labeling of stroke.

In the PC-trial [14], the incidence of stroke was lower than expected which may have induced a type II error. Moreover, the patients enrolled in this study had low risk of stroke compared with patients who undergo closure in routine clinical practice. Lastly, poor patient retention may have induced attrition bias which may have contributed to inaccurate results.

Therefore, based on these randomized controlled trials, PFO closure is currently not recommended for stroke prophylaxis. However, these studies have certain limitations and uncertainty still persists about the optimal management of such patients. Future research may be necessary before definitive statements regarding PFO closure can be advised.

OSA associated cardiovascular effects

OSA may lead to a myriad of cardiovascular disorders including atrial fibrillation, hypertension, congestive heart failure, and diabetes [15–17]. OSA may also be linked to strokes, TIAs, arrhythmias, and ischemic heart disease [15,16,18–20]. The most common arrhythmias associated with OSA is sinus arrest, sinoatrial block, or atrioventricular block which may all lead to ventricular asystole [16]. The mechanism for the arrhythmias is postulated to be increased vagal tone from apnea and hypoxemia [16].

OSA induces the diving reflex with activation of the cardiac vagus nerve promoting bradycardia, sinus arrest, atrioventricular block, and asystole [21]. Sympathetic nervous system stimulation occurring from hypoxia during apneic episodes may induce ventricular arrhythmias [22,23]. OSA may also cause inflammation, endothelial dysfunction, thrombosis, and oxidative stress which may induce cardiovascular disease [21]. Fig. 1 displays the cardiovascular effects of OSA. The American Heart Association and the American College of Cardiology Foundation scientific statement on sleep apnea and cardiovascular disease states that OSA is an underdiagnosed disorder with an increased preponderance in males [21].

Clinical studies of the cardiovascular effects of OSA

A recent meta-analysis by Loke et al. [24] of six studies comprising 8785 patients with OSA showed no statistically significant association with ischemic heart disease (odds ratio (OR) = 1.56, 95% CI = 0.83–2.91). In studies composed of solely male patients (five studies), OSA was found to have a statistically significant association with an increased risk of ischemic heart disease (OR = 1.92, 95% CI = 1.06–3.48). The single study on women reported no significant difference (OR = 0.4, 95% CI = 0.12–1.30). An increased likelihood of stroke or cardiovascular events may occur with higher apnea–hypopnea index values ($p < 0.001$). Therefore, OSA may potentiate the risk for cardiovascular disease and cardiac mortality which highlights the importance of diagnosis and adequate treatment.

In a seven-year retrospective analysis and follow-up study [25], 182 middle-aged patients were evaluated to determine the incidence of cardiovascular disease with or without OSA. The incidence of cardiovascular disease was observed in 22 of 60 patients (36.7%) with OSA compared with eight of 122 patients (6.6%) without OSA ($p < 0.001$). Cardiovascular disease incidence occurred in 56.8% patients who were incompletely treated (continuous positive airway pressure (CPAP), surgery, or oral appliance) for OSA and 6.7% in efficiently treated OSA patients ($p < 0.001$).

The Sleep Heart Health Study [26] was a multicenter, prospective, epidemiological, cohort study which assessed the effects of OSA on coronary heart disease and heart failure. A total of 4422 patients (1927 men; 2495 women) aged ≥40 y who did not have coronary heart disease or heart failure were studied and OSA was a significant predictor of incident coronary heart disease (myocardial infarction (MI), revascularization procedures, or coronary heart disease mortality) only in men ≤70 y of age (adjusted HR = 1.10; 95% CI = 1.00–1.21) per 10-unit increase in apnea–hypopnea index. The adjusted HR was 1.68 (95% CI = 1.02–2.76) for men with AHI ≥30 ($n = 116$, 24 incident events) compared with AHI <5. Therefore, the study supported an enhanced risk of coronary heart disease with severe OSA (AHI > 30). Thus, proper diagnosis and treatment of OSA may prevent future cardiovascular disease.

Clinical studies of patients with PFOs and OSA

A case-controlled study by Shanoudy et al. [27] evaluated 48 male patients with OSA vs. 24 control male patients for the effects of PFOs on hypoxia. The study found that the prevalence of PFOs in patients with OSA was greater compared with controls with no OSA (69% vs. 17%, $p = 0.0001$). Patients with OSA in the presence of a PFO had significant hypoxia compared with the control group (69% vs. 17%, $p = 0.007$). After performing Valsalva maneuver, OSA patients with PFO had increased oxygen desaturations compared with controls (-2.0 ± 1.3 vs. -0.9 ± 0.7, $p = 0.0002$). Furthermore, the estimated pulmonary artery systolic pressure was significantly increased in patients with OSA compared with controls

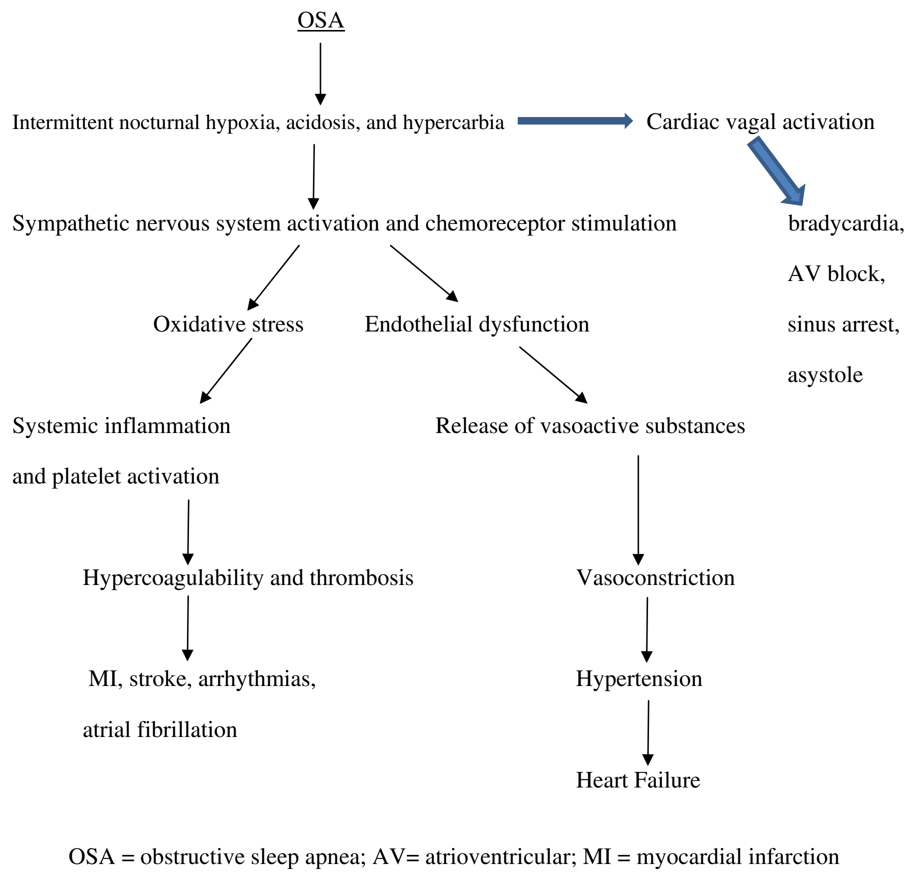

Fig. 1. Physiological effects of OSA and the effects on the cardiovascular system.

(32.0 ± 10.3 mmHg vs. 22.0 ± 6.3 mmHg, $p = 0.003$). Therefore, the study showed an increased prevalence of PFOs in patients with OSA along with an increased incidence of hypoxia during apnea episodes.

A case-controlled study by Johansson et al. [5], evaluated the severity of oxygen desaturation in patients with OSA and the presence of a PFO compared with no PFO. In the group of 209 patients with OSA, the patients with large PFOs had higher oxygen desaturation (9/15, 60%, $p = 0.02$) compared with the low desaturation group (2/15, 13%). The study concluded that oxygen desaturation occurred to a higher degree in OSA patients with PFO who developed frequent respiratory disturbances compared with OSA patients without PFO. However, the case–control study by Lau et al. [28] showed the degree of right to left shunting from a PFO did not significantly impact oxygen desaturation even though an increased prevalence of PFO was found in OSA patients. Such divergent results may be attributed to differing definitions of the size of PFOs. Therefore, closure of PFOs may not necessarily improve oxygen desaturation so medical management may be a safer treatment.

A case report by Pinet et al. [29] showed that one week of CPAP treatment suppressed awake right to left shunting through a PFO in a patient with OSA. The patient had severe OSA with an AHI of 82 per hour. After one week of CPAP treatment, the right to left shunt while awake dramatically decreased from 19% to only 6%. Table 1 lists the clinical studies reporting the effects of OSA in the presence of PFO.

PFO combined with OSA and the association with strokes

PFO and OSA may be associated with cryptogenic stroke [30]. Ozdemir et al. [30], report two cases of patients with OSA who experienced cryptogenic strokes upon awakening. The patients were subsequently discovered to have PFOs.

A cohort study by Guchlerner et al. [31], reports a greater incidence of right to left shunting in the presence of a PFO in 100 consecutive patients with OSA. Such an association may possibly enhance the probability of stroke in these patients. However, no randomized controlled trial or definitive evidence suggests that such a combination unequivocally induces stroke.

PFO closure and the effect on OSA

A case report by Silver et al. [32], showed an improvement of sleep apnea symptoms and apnea frequency quantified on

Table 1
Clinical studies reporting the effects of OSA with PFO.

Study	*n*	Study type	Groups	Endpoints	Results
Johansson et al. [5]	209	Case-controlled	OSA vs. controls	Effects of OSA and PFO on oxygen desaturation	Large PFOs with >oxygen desaturation ($p = 0.02$)
Shanoudy et al. [27]	72	Case-controlled	OSA males; control males with no OSA	Evaluate effects of PFO on hypoxia	PFO >prevalence with OSA (69% vs. 17%, $p = 0.0001$); PFO with OSA >hypoxia (69% vs. 17%; $p = 0.007$)

OSA = obstructive sleep apnea; PFO = patent foramen ovale.

polysomnographic testing after PFO closure of a patient enrolled in a clinical trial. The patient had a drastic reduction in apnea and hypopnea episodes from his first polysomnogram of 181 apneic episodes and eight hypopnea episodes to only 19 apneic episodes and zero hypopneic episodes after PFO closure. Initially, the patient had severe OSA which no longer required the use of CPAP only two months after PFO closure.

A case by Agnoletti et al. [33] reports a patient with OSA and PFO who experienced tiredness, dyspnea, snoring and insomnia with mild exercise who was successfully treated with PFO closure. Afterward, the patients had complete resolution of symptoms. Subsequently, the patient was able to perform strenuous activity without difficulty and maintained normal oxygen saturation during exercise. Table 2 summarizes the case reports of PFO closure in OSA. The prevalence of PFO in OSA is high [27,34].

A recent prospective study by Shaikh et al. [35] evaluated the effects of percutaneous PFO closure in patients with large shunts who had severe OSA. A total of 150 patients were followed for 12 mo, 100 with severe OSA (AHI $= 54 \pm 18$ events/h) and 50 controls (AHI $= 2 \pm 2$ events/h). PFOs were discovered in 43% ($n = 43$) of OSA patients and 30% ($n = 15$) of controls ($p = 0.16$). However, large shunts were present in 18% ($n = 18$) of OSA patients while only 6% ($n = 3$) of controls had large shunts ($p = 0.049$). The presence of small or moderate size shunts did not show any statistically significant variation between OSA patients or controls. Of the 18 patients with large shunts, six underwent percutaneous PFO closure (four patients were previously using CPAP prior to closure). PFO closure did not significantly reduce nocturnal desaturation, AHI, or quality of life. Thus, patients with severe OSA were more likely to have large shunts from their PFO. Nevertheless, PFO closure did not show any significant benefit in reducing nocturnal desaturation or improving hypoxia in patients with OSA. Since the closure group consisted of only six patients, a precise recommendation about PFO closure cannot be derived from these results. Consequently, further studies evaluating patients with concomitant OSA and PFOs are necessary.

Discussion

PFO may co-exist with a greater likelihood in patients with OSA. The severity of OSA may also increase the risk of stroke and cardiovascular disease.

If OSA is diagnosed and patients have a history of cryptogenic stroke, evaluation for PFO may be considered. If a concomitant PFO is found, it may enhance the risk of stroke secondary to an increased probability of right to left shunting from the higher pulmonary pressures with OSA. Whether the PFO should be closed remains unknown since limited data exists and no randomized controlled trials of PFO closure have been performed in patients with OSA. Only two case reports by Silver et al. [32] and Agnoletti et al. [33] show that PFO closure may be beneficial in OSA patients. However, the prospective study by Shaikh et al. [35] showed no significant benefit of PFO closure in six patients with severe OSA. Therefore, routine screening may not provide any clinical benefit.

The CLOSURE I [11] and RESPECT [13] trials have not shown superiority of closure compared with medical therapy in the intention-to-treat analysis. Also, the PC-trial [14] did not show a benefit of PFO closure. Therefore, it is not recommended to close PFOs for stroke prophylaxis.

Further studies are necessary to definitively answer if an association of OSA with PFO increases mortality and whether percutaneous closure may improve outcomes. Thus, future clinical trials evaluating OSA with PFO remains an area of forthcoming research.

Table 2
Case reports showing the effects of PFO closure on OSA.

Case report	n	Groups	Outcomes	Results
Silver et al. [32]	1	PFO with OSA	Sleep apnea symptoms & apnea frequency	Huge reduction of apneic and hypopneic episodes (pre-closure of 181 & 8; post-closure of 19 & 0)
Agnoletti et al. [33]	1	PFO with OSA	OSA symptoms	Resolution of OSA symptoms (tiredness, dyspnea, snoring, and insomnia)

PFO = patent foramen ovale; OSA = obstructive sleep apnea.

Conclusions

OSA is associated with an increased stroke risk and excess cardiovascular mortality. The presence of a PFO has also been associated with cryptogenic stroke. OSA may provide the stimulus which enhances right to left shunting through a PFO, possibly inducing paradoxical thromboembolism. Although epidemiological studies suggest that PFO prevalence may be higher in OSA subjects, a clinically important interaction between the two conditions remains inconclusive. If patients have PFO with OSA, meticulous follow-up for the negative consequences of OSA and PFO such as cryptogenic stroke may allow the contemplation of antiplatelet or anticoagulant therapy. Only case reports by Silver et al. [32] and Agnoletti et al. [33] showed that PFO closure reduced sleep apnea episodes or symptoms. However, no randomized controlled trial of PFO closure in OSA patients has been conducted. Therefore, the role of percutaneous closure remains unknown since no definitive data exists which highlights the importance of future research in OSA with PFO.

OSA may be present in patients with refractory hypertension (especially nocturnal hypertension), daytime hypersomnolence, nocturnal arrhythmias, nocturnal ischemia, or stroke [16]. Early diagnosis and prompt initiation of medical therapy may mitigate the adverse cardiovascular effects from the concomitant presence of PFO with OSA. Further studies are necessary to define a direct relationship between the adverse effects associated with PFO and OSA before precise recommendations may be suggested regarding medical vs. percutaneous closure of PFOs.

Practice points

1) The presence of PFO with OSA may increase the risk of stroke.
2) The CLOSURE I [11], RESPECT [13] (intention-to-treat analysis), and PC-trial [14] did not show a statistically significant benefit for PFO closure. Therefore, PFO closure is not recommended for stroke prophylaxis.
3) No randomized controlled trial has been conducted to specifically assess the benefits of PFO closure in OSA patients. Whether PFO closure in OSA should be performed remains unknown so invasive therapy is not recommended.

Research agenda

1) Research involving the cerebrovascular effects of the concomitant presence of a PFO with OSA requires further study.
2) Further research evaluating the significance of the presence of a PFO with OSA on cardiovascular health may provide important information which could impact numerous patients and the medical community.
3) No randomized controlled trial has been conducted to assess the benefits of PFO closure in OSA patients. Thus, the unambiguous benefit of PFO closure in OSA patients is unknown which suggests an area of future research.

Disclosures

No conflicts of interest or financial support was provided.

Acknowledgments

None.

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* The most important references are denoted by an asterisk.